Liabeuf, S., Sajjad, A., Kramer, A., Bieber, B., McCullough, K., Pisoni, R., Caskey, F., Combe, C., Robinson, B. M., Jager, K. J., & Massy, Z. A. (2019). Guideline attainment and morbidity/mortality rates in a large cohort of European hemodialysis patients (EURODOPPS). *Nephrology Dialysis Transplantation*, [gfz049]. https://doi.org/10.1093/ndt/gfz049

Guideline attainment and morbi-mortality in a large cohort of European hemodialysis patients (EURODOPPS)

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Running head : Guideline targets and outcomes in European dialysis patients

Abstract

Background: Hemodialysis patients experience a wide variety of intermediate complications, such as anemia, hypertension and mineral bone disease (MBD). We aimed to assess the risk of death and hospital admissions as a function of the simultaneous attainment of different guideline targets (for hypertension, anemia and MBD) in a large European cohort of dialysis patients.

Methods: EURODOPPS is part of the DOPPS international, prospective cohort study of adult, in-center hemodialysis patients for whom clinical data are extracted from medical records. In the present analysis, 6317 patients from seven European countries were included between 2009 and 2011. The percentages of patients treated according to the international guidelines on anemia, hypertension, and MBD were determined. The overall degree of guideline attainment was considered to be high if four or all five of the evaluated targets were attained, moderate if two or three targets were attained, and low if less than two targets were attained. Fully adjusted multivariate Cox models were used to investigate the relationship of target attainment with mortality and first hospital admission.

Results: At baseline, the degree of target attainment was low in 1751 patients (28%), moderate in 3803 (60%) and high in 763 (12%). In the fully adjusted model using time-dependent covariates, low attainment was associated with higher all-cause mortality (hazard ratio [95% confidence interval]: 1.19 [1.05–1.34]) and high attainment was associated with lower all-cause mortality (0.82 [0.68–0.99]). In a similar model that additionally accounted for death as a competing risk, low and high attainment were not associated with hospital admission.

Conclusion: In a large international cohort of dialysis patients, we have shown that more stringent application of guidelines is associated with lower mortality.

Keywords: Guideline; target; attainment; hemodialysis; mortality; hospital admission

INTRODUCTION

Chronic kidney disease (CKD) is a major global health problem, in view of its high prevalence and associated complications. [1] The number of deaths directly attributable to CKD rose by 36% between 1990 and 2013. [2] The progression of CKD is associated with an elevated incidence of serious complications, including cardiovascular disease, anemia and mineral bone disease (MBD). Hence, CKD patients should be screened for these complications and then be treated appropriately. Furthermore, reduction of the corresponding morbidity and mortality rates requires a multidisciplinary approach.

Various international guidelines have focused on reducing the complications of CKD. [3],[4] In hemodialysis patients, we recently highlighted (i) a low overall level of guideline target attainment in Europe and (ii) substantial differences between European countries in this respect. [5] Indeed, hemodialysis patients experience various concomitant complications, such as MBD (including abnormalities of calcium, phosphate or parathyroid hormone (PTH)), anemia and hypertension. [6] Considering any of these conditions in isolation is inconsistent with the clinical situations that physicians encounter in practice. Most epidemiologic studies have sought to assess the prognostic value of a single complication, such as hypertension or hyperphosphatemia. [7] In contrast, there are few studies that focus on CKD-related metabolic complications as a whole and their impact on hard outcomes. [8]

We therefore sought to assess survival and hospitalization as a function of the degree of guideline target attainment (hypertension, anemia and MBD), using data from a large, prospective, European study of a cohort of adult in-center hemodialysis patients.

METHODS

Study population

The DOPPS is an international, prospective study of a cohort of adult (aged 18 and over) in-center hemodialysis patients. The study is currently in its sixth phase (DOPPS 6). Details of the study's design have been reported elsewhere. [9] The present analysis included 6317 EURODOPPS participants from seven European countries (Belgium, France, Germany, Italy, Spain, Sweden and the UK) in DOPPS phase 4 (2009-2011). The study was approved by a central investigational review board and by the appropriate local investigational review boards.

Data collection

We assessed data on five targets: blood pressure, and serum levels of phosphate, hemoglobin, PTH, and calcium. For each investigated parameter, the selected target ranges (extracted from the international KDOQI or KDIGO guidelines and (if available) the European Renal Best Practice guidelines at the time of the study (2009-2011)) are given in Table 1. For each patient, we calculated how many of the targets had been met and then graded the overall degree of target attainment. The overall degree of target attainment was considered to be high if 4 or 5 targets were attained, moderate if 2 or 3 targets were attained, and low if less than 2 targets were attained. Data on demographic parameters, comorbidities, laboratory test values and dialysis were extracted from the patients' medical records at study entry. Follow-up information was obtained every 4 months and included laboratory measurements and dates of and diagnoses associated with patient hospitalization. Mortality data were collected continuously during the study follow-up period. [9], [10]

Statistical analyses

We used Cox proportional-hazards regression models with time-dependent covariates to relate all-cause mortality to the 4-month running values of overall target attainment in dialysis patients [11,12]. In order to account for death as a competing risk [13], we also used a Fine and Gray model to evaluate the association between the 4-month running values of overall target attainment and first hospital admission [14]. The time at risk ended upon death, first hospital admission, discharge from the facility (due to transfer or a change in the type of renal replacement therapy) plus 7 days, loss to follow-up, transplantation, or the end of the study phase (whichever occurred first).

To check for reverse causality, the second last follow-up laboratory value for each target was used rather than the last assessment to define "target attainment" (time-lagged covariate). We used the second last follow-up laboratory value because we thought that using the last assessment might lead (in some cases) to an evaluation of parameters in the "acute phase" of the disease and thus might overestimate the off-target patients. [12] The proportional hazard assumption was evaluated using Schoenfeld residuals. [11] Time to death and first hospital admission were analyzed without adjustment (Model 0), and with adjustment for age, gender, race (Caucasian vs. non-Caucasian), country, smoking status (active vs. former smoker), time on dialysis, single pool Kt/V, and body mass index. Model 2 was additionally adjusted for the presence or absence of 13 comorbid conditions (the usual adjustment covariates used in DOPPS studies): diabetes mellitus, cancer (excluding skin), HIV, lung disease, psychiatric disorders, gastrointestinal bleeding, neurological disease, recurrent cellulitis, hypertension, congestive heart failure, cerebrovascular disease, coronary

heart disease, and other cardiovascular diseases. When studying the associations with individual targets and outcomes, we further adjusted for each target in a separate model (Model 3). Sensitivity analysis were performed excluding blood pressure target from the overall target attainment. We also calculated the variance inflation factor to examine multicollinearity between the predictors.

The variance inflation factor was <4.0 for all predictors in the models used for both mortality and hospitalization analyses, which indicated that there was limited multicollinearity and thus did not warrant further investigation.

Missing values for exposure and confounding variables were imputed by multiple imputation by chained equations in which 20 completed data sets were generated and analyzed with standard combination rules for multiple imputation. Each variable was used as a predictor in the imputation model. Variance inflation factor was calculated by taking the mean for the imputed results. We assumed that the data were missing at random.

Our results are reported as the hazard ratio (HR) [95% confidence interval (CI)]. The threshold for statistical significance was set to $p<0.05$. All statistical analyses were performed using STATA/MP software (version 14.2, Stata Corp, College Station, TX).

RESULTS

Characteristics of the study population

In the present analysis, 6317 hemodialysis patients from seven European countries were included between 2009 and 2011; this total comprised 300 (4.8%) incident patients (i.e. hemodialysis for 30 days or less) and 6017 (95.3%) prevalent patients (i.e. hemodialysis for over 30 days). The study population's baseline demographic and clinical characteristics according to the overall degree of target attainment are summarized in Table 2. The mean ± standard deviation (SD) age was 65.5 ± 15.0. More than half of the patients were men (60.8%, n=3840), and the great majority of the patients were of Caucasian origin (93.4%, n=5898). About one third of the patients were diabetic (36.5%, n=2304), and 11.2% (n=708) were current smokers. At baseline, attainment of guidelines was considered to be low in 1751 (27.7%) patients, moderate in 3803 (60.2%) and high in 763 (12.1%). On average, patients in the "high attainment" group were older, less likely to be active smokers, and had been on dialysis longer than patients in the "moderate attainment" and "low attainment" groups. There

were no other significant differences in dialysis characteristics or comorbidities according to the degree of target attainment.

All-cause mortality

The total number of person-years in the analysis of all-cause mortality was 9119.3 (median (25^{th}-75^{th} percentile) follow-up time: 1.38 (0.68-2.27) years), during which time a total of 1328 patients died, the other 4989 patients are censored (3779 due to end of follow-up period, 499 due to transplantation, 55 due to transfer to other dialysis modality, 27 due to recovery renal function and 629 were lost to follow-up).

Table 3 shows the HRs for all-cause mortality according to the overall degree of guidelines target attainment. The proportional hazards assumption was met for all associations tested. In the fully adjusted model using time-varying covariates, a low degree of target attainment at baseline was associated with significantly higher all-cause mortality (HR [95%CI] = 1.19 [1.05–1.34] (Table 3), whereas a high degree of target attainment was associated with significantly lower all-cause mortality (HR [95%CI] = 0.82 [0.68–0.99]). The decrease in HR as a function of the degree of target attainment appeared to be gradual (Supplementary Table 1).

For individual targets, anemia, failure to attain PTH targets and failure to attain calcium targets (excessively low or high values) was associated with increased mortality. In contrast, elevated blood pressure levels were associated with lower mortality (Supplementary Table 2).

In a sensitivity analysis, exclusion of blood pressure target from the overall target confirmed that a low degree of overall target attainment was associated with worse survival (HR [95%CI] = 1.35 [1.21–1.51] (Supplementary Table 3).

Hospitalization

Over a median (25^{th}-75^{th} percentile) follow-up period of 6.6 (2.6-15.1) months, a total of 3695 first hospital admissions were recorded, 342 patients died (competing event), the other 2278 patients are censored (1602 due to end of follow-up period, 291 due to transplantation, 29 due to transfer to other dialysis modality, 18 due to recovery renal function and 338 were lost to follow-up). Supplementary Table 4 shows the results of a time-varying analysis (accounting for death as a competing risk) of the associations between the attainment of individual guideline targets and the first hospital admission. In the fully adjusted model, neither low nor high degrees of target attainment at baseline were associated with the risk of hospitalization (Table 4 and Supplementary Table 5).

DISCUSSION

In a large, representative population of hemodialysis patients in seven European countries, we assess survival and hospitalization as a function of the degree of guideline target attainment based on international guidelines for hypertension, anemia and CKD-MBD published during DOPPS phase 4 (2009-2011). A high overall degree of target attainment was independently associated with better survival, and this association increased gradually as a function of degree of target attainment.

A key feature of the present analysis is that we evaluated several different CKD-related metabolic complications; this approach more closely mirrors clinical practice, where patients frequently display several complications concomitantly. Indeed, most epidemiologic studies have evaluated the association of a single complication or a single drug class on hard endpoints such as mortality. [15],[16] A global approach (i.e. simultaneously considering the various CKD-related metabolic complications and their respective associations on hard outcomes) is more relevant with regard to everyday clinical practice. Even though the parameters studied here constitute intermediate outcomes, they are important in a CKD setting and can be modulated using pharmacological therapy. Hence, this type of analysis is particularly relevant because clinical trials based on hard clinical outcomes are relatively infrequent in CKD patients. [17], [18]

In the field of CKD, it is relatively difficult to draft detailed guidelines based on strong scientific evidence. This might affect the extent to which clinicians agree with and adopt a given guideline. [18] Even though the guidelines studied here may be based on relatively low levels of evidence, our present findings suggest that target attainment could be associated with significantly improve outcomes even if causal relationship can not be shown in this kind of analysis. In the present study, only 12% of the patients attained 4 or 5 targets, so there is definitely room for improvement in target attainment and outcomes across Europe. However, target attainment might face several obstacles. Indeed, certain patient characteristics might explain the poor target attainment in the 28% of patients in the “low attainment” group. In a patient with several comorbidities and a short life expectancy, one can presume that the attainment of clinical metabolic targets is not the nephrologist’s priority for care, and attainment may turn out to be very difficult or impossible. In contrast, for a young patient expecting to undergo kidney transplantation, attainment of clinical metabolic targets will be strongly pursued. Furthermore, target attainment is known to be associated with dialysis vintage, as patients need time to reach target levels. The current study cohort also included

incident patients and patients who had not been on hemodialysis for very long at the time of study enrollment, which may have reduced target attainment. Lastly, poor adherence to medications (and particularly phosphate binders) and dietary restrictions is frequent among hemodialysis patients [20,21,22,23].

In the present study, we found that high blood pressure levels were associated with lower mortality. This may be because low blood pressure levels reflect heart failure, the prevalence of which is high among patients with CKD [19]. This constituted a potential source of bias, since as patients with heart failure (characterized by low blood pressure) might have a higher risk of death. After excluding the blood pressure target from the overall target attainment, we observed a 35% increase in the risk of death in the low target attainment group versus the moderate target attainment group; hence, one could argue that inclusion of a blood pressure target dampens the influence on outcomes.

The findings of the present study suggest that a more stringent application of guidelines is associated with lower mortality. How dialysis units might achieve these targets within their current care systems should be debated. In the US, the Centers for Medicare and Medicaid Services and commercial insurers use clinical performance measures (CPMs) to assess the quality of care [24]. In this quality incentive program, a portion of the payment made to a dialysis facility is linked to the latter's CPMs. Furthermore, the publication of CPMs provides all stakeholders (including patients and physicians) information on performance quality that can be useful when selecting caregivers and facilities for referral and care. [24] However, not all countries operate quality incentive programs, and the latter's impacts on guideline attainment at dialysis facilities have yet to be evaluated.

The present study had several strengths: firstly, our analysis of hard outcomes usefully complements our previous report on the low overall degree of target attainment in EURODOPPS patients and the differences between European countries in this respect. [5] Secondly, we performed Cox analyses with time-varying covariates because a baseline analysis evaluates an effect at a single moment in time, which may not be of value from a clinical point of view. [23] In contrast, a time-varying covariate approach enables evaluation of any potential effects of target attainment and covariate changes over time. Some limitations merit consideration: firstly, this study was based on observational data, and patients were not randomized so no causal relationships can be inferred. Patients in the "higher guideline target attainment" were older and had been on dialysis for a longer time, so one cannot rule out a survival bias. Furthermore, residual cofounding can never be ruled out. A patient's ability to attain guideline targets might also result from his/her general health status, which is difficult

to take into account in statistical models. Our analyses were extensively adjusted (e.g. for age, comorbidities, and country) to minimize the risk of residual cofounding. However, confounding by indication (inherent to the observational nature of the study) can not be accounted for in this kind of analysis. Indeed, the results of this study should be interpreted in light of this, as the physician may have been less stringent in adhering to guidelines in patients for whom he/she expected to have a poor survival. This may be a partial explanation for our findings. Secondly, we selected a set of biological variables that could be modulated by pharmacological agents and/or dietary restrictions and for which detailed data were collected in the DOPPS; however, also other variables not studied here might have had an impact on mortality and hospitalization. Other important guideline targets (such as functional vascular access) were not evaluated in the present study, although the single pool Kt/V was >1.2 and did not differ significantly when comparing the three groups (thus ruling out a potential under-dialysis issue). [24] Furthermore, we did not have data on malnutrition, achievement of dry weight, the frequency of intradialytic hypotension, and the level of ultrafiltration – all factors that might modulate outcomes in hemodialysis patients, were not available. Thirdly, we were unable to assess the patients' adherence to treatment (including medications and dietary restrictions) – a factor that might have a major effect on target attainment.

In conclusion, our analysis of data from a large cohort study of European hemodialysis patients showed that the attainment of targets according to international guidelines is associated with a lower risk of all-cause mortality.

ACKNOWLEDGEMENTS

This article was written by S.L., A.S., A.K., B.B., K.M., R.P., F.C., C.C., B.M.R., K.J.J, Z.A.M. on behalf of the EURODOPPS and the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Registry which is an official body of the ERA-EDTA. The EURODOPPS Initiative is funded by the ERA-EDTA and the DOPPS Program. In turn, the DOPPS program is funded by Amgen, Kyowa Hakko Kirin, AbbVie Inc., Sanofi Renal, Baxter Healthcare, and Vifor Fresenius Medical Care Renal Pharma, Ltd. Additional support for specific projects and countries is also provided by the ERA-EDTA, Keryx Biopharmaceuticals, Inc., Merck Sharp & Dohme Corp., Proteon Therapeutics, Relypsa, and F. Hoffmann-LaRoche Ltd.; in Canada by Amgen, BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support); in Germany by Hexal, DGfN,

Shire, WiNe Institute; for PDOPPS in Japan by the Japanese Society for Peritoneal Dialysis (JSPD). All support is provided without restrictions on publications. Grants are made to Arbor Research Collaborative for Health and not to individual investigators.

S. Liabeuf's clinical fellowships are provided by ERA-EDTA. The authors alone are responsible for the reporting and interpretation of EURODOPPS data used in the publication and these reports do not necessarily represent the decisions or policies of the ERA-EDTA or the DOPPS Program.

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Table 1: Definition of clinical targets and clinical biochemistry targets

	Target
CKD-MBD(27,28)	1. A serum phosphate level between 3.5 and 5.5 mg/dl 2. An intact PTH level between 150 and 600 pg/ml 3. A serum calcium level between 8.4 and 10.2 mg/dl
Hypertension (29)	4. A mean of three blood pressure measurements <140/90 mmHg (pre-HD) and <130/80 mmHg (post-HD)
Anemia (30)	5. A serum hemoglobin level between 11 and 12 g/dl

Abbreviations: CKD-MBD, chronic kidney disease –mineral and bone disease; HD, hemodialysis; PTH, parathyroid hormone.

Table 2: Demographic characteristics, according to the degree of target attainment

	Low attainment N=1751	Moderate attainment N= 3803	High attainment N=763	P value
Age, years (IQR)	67.0 (22.0)	68.0 (21.0)	72.0 (18.0)	<0.001
Male gender, n (%)	1069 (61.1)	2323 (61.1)	448 (58.7)	0.447
Race (Caucasian), n (%)	1618 (92.4)	3553 (93.4)	727 (95.3)	0.028
Body mass index, kg/m^2 (SD)	25.6 (5.4)	26.0 (5.4)	26.3 (5.1)	0.012
Smoking (active), n %	221 (12.6)	428 (11.3)	59 (7.7)	<0.001
Time on dialysis, yr (IQR)	0.9 (3.6)	1.7 (4.5)	2.4 (4.7)	<0.001
Single pool Kt/V (SD)	1.5 (0.3)	1.5 (0.3)	1.5 (0.3)	0.011
Parathyroid hormone pg/ml (IQR)	129 (391)	228 (247)	269 (188)	<0.001
Hemoglobin g/dL (SD)	11.0 (1.7)	11.3 (1.4)	11.5 (0.9)	<0.001
Calcium, g/dL (SD)	8.8 (1.6)	9.0 (1.2)	9.1 (0.7)	<0.001
Phosphate, g/dL (SD)	5.4 (2.1)	4.9 (1.5)	4.6 (0.9)	<0.001
Pre-dialysis systolic BP, mmHg (SD)	146.7 (20.0)	137.0 (21.8)	125.6 (19.5)	<0.001
Pre-dialysis diastolic BP, mmHg (SD)	75.3 (13.6)	71.1 (13.2)	66.7 (11.8)	<0.001
Post-dialysis systolic BP, mmHg (SD)	142.3 (21.1)	132.3 (22.9)	119.6 (19.4)	<0.001
Post-dialysis diastolic BP, mmHg (SD)	74.2 (13.2)	69.9 (13.2)	65.1 (11.6)	<0.001
Diabetes mellitus, n (%)	648 (37.0)	1377 (36.2)	279 (36.6)	0.864
Cancer (excluding skin), n (%)	317 (18.1)	612 (16.1)	142 (18.6)	0.077
HIV, n (%)	12 (0.7)	19 (0.5)	2 (0.3)	0.382
Lung disease, n (%)	226 (12.9)	522 (13.7)	121 (15.9)	0.142
Psychiatric disorder, n (%)	320 (18.3)	617 (16.2)	143 (18.7)	0.074
GI bleeding, n (%)	99 (5.7)	187 (4.9)	24 (3.2)	0.028
Neurological disease, n (%)	221 (12.6)	458 (12.0)	96 (12.6)	0.798
Recurrent cellulitis, n (%)	170 (9.7)	378 (9.9)	72 (9.4)	0.899
Hypertension, n (%)	1515 (86.5)	3240 (85.2)	635 (83.2)	0.093
Antihypertensive medication, n (%)*	1368 (78.1)	2852 (75.0)	519 (68.0)	<0.001
Congestive heart failure, n (%)	311 (17.8)	778 (20.5)	177 (23.2)	0.004
Cerebrovascular disease, n (%)	288 (16.5)	664 (17.5)	136 (17.8)	0.582
Coronary heart disease, n (%)	596 (34.0)	1390 (36.6)	300 (39.3)	0.031
Other cardiovascular diseases, n (%)	463 (26.4)	1242 (32.7)	302 (39.6)	<0.001

Values are percentages for categorical variables.

Differences in patient characteristics for the target attainment groups were evaluated using $\chi 2$ tests for categorical variables, ANOVA (analysis of variance) for normally distributed continuous variables and Kruskal-Wallis test for non-normally distributed continuous variables.

Mean (SD) for continuous normally distributed variables.

Median (IQR) for continuous, non-normally distributed variables.

*Antihypertensive medication included: ACE inhibitors, Angiotensin II receptor blockers, Renin inhibitors, Calcium channel blockers, Aldosterone antagonists, Beta blockers, Diuretics, Peripheral adrenergic inhibitors, Central-acting alpha 2 antagonists and Vasodilators

Table 3: Association between the overall degree of target attainment and mortality during the study follow-up period (with moderate attainment as the reference)

Target attainment	**Time-varying covariates** Number of events =1328		
	Model 0 HR [95% CI]	**Model 1** HR [95% CI]	**Model 2** HR [95% CI]
Low attainment	**1.64 [1.46, 1.85]**	**1.18 [1.05, 1.33]**	**1.19 [1.06, 1.34]**
Moderate attainment	Reference	Reference	Reference
High attainment	**0.67 [0.56, 0.81]**	**0.82 [0.68, 0.99]**	**0.82 [0.68, 0.99]**

Model 0: unadjusted

Model 1: adjusted for age, gender, race, country, time on dialysis, smoking, body mass index, single pool Kt/V

Model 2: additionally adjusted for 13 comorbid diseases (diabetes mellitus, cancer (excluding skin), HIV, lung disease, psychiatric disorders, gastrointestinal bleeding, neurological disease, recurrent cellulitis, hypertension, congestive heart failure, cerebrovascular disease, coronary heart disease, and other cardiovascular diseases).

Table 4: Association between the overall degree of target attainment and hospitalization during the study follow-up period (with moderate attainment as the reference), using a competing risk model

Target attainment	**Time-varying covariates** Number of events = 3695		
	Model 0 HR [95% CI]	**Model 1** HR [95% CI]	**Model 2** HR [95% CI]
Low attainment	**3.13 [2.94, 3.33]**	1.07 [0.97, 1.19]	1.08 [0.97, 1.19]
Moderate attainment	Reference	Reference	Reference
High attainment	**0.84 [0.75, 0.94]**	1.13 [0.99, 1.30]	1.13 [0.99, 1.30]

Model 0: unadjusted

Model 1: adjusted for age, gender, race, country, time on dialysis, smoking, body mass index, single pool Kt/V

Model 2: additionally adjusted for 13 comorbid diseases (diabetes mellitus, cancer (excluding skin), HIV, lung disease, psychiatric disorders, gastrointestinal bleeding, neurological disease, recurrent cellulitis, hypertension, congestive heart failure, cerebrovascular disease, coronary heart disease, and other cardiovascular diseases).

Supplementary Table 1: Association between the overall degree of target attainment and mortality during the study follow-up period (with low attainment as the reference)

Target attainment	**Time-varying covariates** Number of events = 1328		
	Model 0 HR [95% CI]	**Model 1** HR [95% CI]	**Model 2** HR [95% CI]
Low attainment	Reference	Reference	Reference
Moderate attainment	**0.61 [0.54, 0.68]**	**0.85 [0.75, 0.95]**	**0.84 [0.75, 0.95]**
High attainment	**0.41 [0.34, 0.50]**	**0.70 [0.57, 0.85]**	**0.69 [0.56, 0.84]**

Model 0: unadjusted

Model 1: adjusted for age, gender, race, country, time on dialysis, smoking, body mass index, single pool Kt/V

Model 2: additionally adjusted for 13 comorbid diseases (diabetes mellitus, cancer (excluding skin), HIV, lung disease, psychiatric disorders, gastrointestinal bleeding, neurological disease, recurrent cellulitis, hypertension, congestive heart failure, cerebrovascular disease, coronary heart disease, and other cardiovascular diseases).

Supplementary Table 2: Association between the attainment of individual targets and mortality
Number of events=1328.

Target attainment	**Model 0**	**Model 1**	**Model 2**	**Model 3**
		HR [95% CI]	HR [95% CI]	HR [95% CI]
PTH on target (150≤PTH<600)	Reference	Reference	Reference	Reference
Hypoparathyroidism (PTH<150)	**1.57 [1.36, 1.81]**	**1.32 [1.15, 1.53]**	**1.29 [1.12, 1.49]**	**1.22 [1.06, 1.42]**
Hyperparathyroidism (PTH≥600)	**3.30 [2.90, 3.75]**	**1.34 [1.18, 1.53]**	**1.38 [1.21, 1.57]**	**1.43 [1.25, 1.63]**
Phosphate on target (3.5≤PO_4<5.5)	Reference	Reference	Reference	Reference
Hypophosphatemia (PO_4<3.5)	**1.56 [1.36, 1.78]**	**1.37 [1.20, 1.58]**	**1.31 [1.14, 1.50]**	1.15 [0.99, 1.32]
Hyperphosphatemia (PO_4≥5.5)	**1.19 [1.05, 1.34]**	1.08 [0.95, 1.23]	1.09 [0.96, 1.24]	1.09 [0.95, 1.25]
Calcium on target (8.4≤Ca<10.2)	Reference	Reference	Reference	Reference
Hypocalcemia (Ca<8.4)	**1.50 [1.30, 1.72]**	**1.61 [1.39, 1.85]**	**1.54 [1.34, 1.78]**	**1.38 [1.19, 1.59]**
Hypercalcemia (Ca≥10.2)	**1.64 [1.43, 1.88]**	1.14 [0.99, 1.31]	1.13 [0.98, 1.30]	**1.19 [1.03, 1.38]**
Hemoglobin (Hb) on target (11 ≤ Hb <12)	Reference	Reference	Reference	Reference
Hb <9	**3.56 [2.96, 4.28]**	**2.57 [2.13, 3.10]**	**2.44 [2.02, 2.95]**	**2.19 [1.81, 2.65]**
9 ≤ Hb < 11	**1.67 [1.45, 1.93]**	**1.51 [1.31, 1.75]**	**1.50 [1.30, 1.73]**	**1.46 [1.26, 1.69]**
12 ≤ Hb < 13 g/dl	**0.80 [0.67, 0.96]**	**0.80 [0.67, 0.96]**	**0.82 [0.69, 0.99]**	**0.81 [0.68, 0.98]**
Hb ≥ 13 g/d	1.14 [0.95, 1.38]	0.84 [0.70, 1.02]	0.85 [0.70, 1.02]	**0.79 [0.65, 0.96]**
Blood pressure on target	Reference	Reference	Reference	Reference
Hypertension (pre-dialysis systolic ≥140 or pre-dialysis diastolic ≥90 or post-dialysis systolic ≥130 or post-dialysis diastolic ≥80	**0.77 [0.69, 0.86]**	**0.68 [0.61, 0.76]**	**0.71 [0.63, 0.79]**	**0.74 [0.66, 0.83]**

Model 0: Unadjusted

Model 1: adjusted for age, gender, race, country, time on dialysis, smoking, body mass index, single pool kt/V

Model 2: additionally adjusted for 13 comorbid diseases

Model 3: additionally adjusted for each target

Supplementary Table 3: Association between the overall degree of target attainment (excluding blood pressure target) and mortality during the study follow-up period (with moderate attainment as the reference)

Target attainment	**Time-varying covariates** Number of events = 1328		
	Model 0 HR [95% CI]	**Model 1** HR [95% CI]	**Model 2** HR [95% CI]
Low attainment	**1.96 [1.75, 2.18]**	**1.38 [1.23, 1.54]**	**1.35 [1.21, 1.51]**
Moderate attainment	Reference	Reference	Reference
High attainment	**0.51 [0.36, 0.73]**	**0.68 [0.47, 0.97]**	0.70 [0.49, 1.00]

Model 0: unadjusted

Model 1: adjusted for age, gender, race, country, time on dialysis, smoking, body mass index, single pool Kt/V

Model 2: additionally adjusted for 13 comorbid diseases (diabetes mellitus, cancer (excluding skin), HIV, lung disease, psychiatric disorders, gastrointestinal bleeding, neurological disease, recurrent cellulitis, hypertension, congestive heart failure, cerebrovascular disease, coronary heart disease, and other cardiovascular diseases).

Supplementary Table 4: Association between attainment of individual targets and first hospitalization using a competitive risk model. Number of events: 3695

Target attainment	**Model 0**	**Model 1**	**Model 2**	**Model 3**
		HR [95% CI]	HR [95% CI]	HR [95% CI]
PTH on target (150≤PTH<600)	Reference	Reference	Reference	Reference
Hypoparathyroidism (PTH<150)	1.01 [0.93, 1.11]	**0.84 [0.75, 0.95]**	**0.84 [0.74, 0.94]**	**0.85 [0.75, 0.96]**
Hyperparathyroidism (PTH≥600)	**3.43 [3.19, 3.68]**	**0.80 [0.72, 0.89]**	**0.80 [0.72, 0.89]**	**0.67 [0.59, 0.75]**
Phosphate on target (3.5≤PO_4<5.5)	Reference	Reference	Reference	Reference
Hypophosphatemia (PO_4<3.5)	1.02 [0.92, 1.14]	0.95 [0.82, 1.10]	0.95 [0.82, 1.10]	0.97 [0.84, 1.12]
Hyperphosphatemia (PO_4≥5.5)	**2.61 [2.45, 2.79]**	1.10 [0.99, 1.22]	**1.11 [1.00, 1.22]**	1.03 [0.93, 1.14]
Calcium on target (8.4≤Ca<10.2)	Reference	Reference	Reference	Reference
Hypocalcemia (Ca<8.4)	1.04 [0.94, 1.15]	1.08 [0.93, 1.26]	1.10 [0.95, 1.28]	1.10 [0.95, 1.27]
Hypercalcemia (Ca≥10.2)	**3.95 [3.67, 4.25]**	**1.27 [1.13, 1.41]**	**1.28 [1.15, 1.43]**	**1.27 [1.13, 1.44]**
Hemoglobin (Hb) on target (11 ≤ Hb <12)	Reference	Reference	Reference	Reference
Hb <9	**1.35 [1.11, 1.64]**	0.79 [0.59, 1.06]	0.81 [0.61, 1.09]	0.88 [0.66, 1.17]
9 ≤ Hb < 11	1.09 [0.98, 1.20]	0.91 [0.80, 1.04]	0.92 [0.81, 1.05]	0.93 [0.82, 1.06]
12 ≤ Hb < 13 g/dl	0.97 [0.87, 1.07]	0.93 [0.81, 1.06]	0.93 [0.81, 1.06]	0.93 [0.81, 1.06]
Hb ≥ 13 g/d	**3.87 [3.57, 4.21]**	**1.16 [1.02, 1.32]**	**1.18 [1.04, 1.33]**	**1.18 [1.03, 1.35]**
Blood pressure on target	Reference	Reference	Reference	Reference
Hypertension (pre-dialysis systolic ≥140 or pre-dialysis diastolic ≥90 or post-dialysis systolic ≥130 or post-dialysis diastolic ≥80	**1.99 [1.85, 2.13]**	**1.15 [1.04, 1.27]**	**1.14 [1.03, 1.27]**	1.07 [0.97, 1.19]

Model 0: unadjusted

Model 1: adjusted for age, gender, race, country, time on dialysis, smoking, body mass index, single pool Kt/V

Model 2: additionally adjusted for 13 comorbid diseases (diabetes mellitus, cancer (excluding skin), HIV, lung disease, psychiatric disorders, gastrointestinal bleeding, neurological disease, recurrent cellulitis, hypertension, congestive heart failure, cerebrovascular disease, coronary heart disease, and other cardiovascular diseases).

Model 3: additionally adjusted for each target

Supplementary Table 5: Association between the overall degree of target attainment and hospitalization during the study follow-up period (with low attainment as the reference), using a competiting risk model.

Target attainment	**Time-varying covariates** Number of events = 1328		
	Model 0 HR [95% CI]	**Model 1** HR [95% CI]	**Model 2** HR [95% CI]
Low attainment	Reference	Reference	Reference
Moderate attainment	**0.32 [0.30, 0.34]**	0.93 [0.84, 1.03]	0.93 [0.84, 1.03]
High attainment	**0.27 [0.24, 0.30]**	1.06 [0.91, 1.23]	1.05 [0.90, 1.22]

Model 0: unadjusted

Model 1: adjusted for age, gender, race, country, time on dialysis, smoking, body mass index, single pool Kt/V

Model 2: additionally adjusted for 13 comorbid diseases (diabetes mellitus, cancer (excluding skin), HIV, lung disease, psychiatric disorders, gastrointestinal bleeding, neurological disease, recurrent cellulitis, hypertension, congestive heart failure, cerebrovascular disease, coronary heart disease, and other cardiovascular diseases).